临床研究

TNM Ⅰ~Ⅲ期结直肠癌病人治疗前血清癌胚抗原水平与预后的关系

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摘要:目的 评价治疗前癌胚抗原水平与Ⅰ~Ⅲ期结直肠癌病人预后的关系。**方法** 回顾性分析广州市第一人民医院2003年1月~2013年12月收治的393例结直肠癌病人的临床病例资料,以5 ng/mL为标准分为未升高组(CEA<5 ng/mL)257例,升高组(CEA≥5 ng /mL)136例,比较两组病人临床、病理数据及预后。**结果** 两组病人的肿瘤大小、分化程度、淋巴结转移的差异有统计学意义(*P*<0.05)。Cox比例风险模型提示,术前高CEA水平是影响病人术后生存及复发的危险因素,升高组病人死亡及复发风险分别提高1.59及1.89倍。在随访期内,升高组的死亡率为28.7%、复发率为32.4%,均高于未升高组的19.8%和19.1%,差异有统计学意义(*P*<0.05),升高组病人的累积总生存率及累积无瘤生存率明显低于未升高组病人,差异有统计学意义(*P*<0.05),在TNM Ⅲ期病人中,升高组病人的累积总生存率及累积无瘤生存率明显低于未升高组病人,差异有统计学意义(*P*<0.05)。**结论** 在TNM分期系统中加入治疗前癌胚抗原水平后可产生新的生存及复发数据,指导临床医生更准确的判断病人的预后。

关键词:结直肠癌;治疗前癌胚抗原水平;预后

Prognostic value of preoperative carcinoembryonic antigen level in patients with stage I-III colorectal cancer

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Abstract: Objective To evaluate the prognostic value of preoperative serum carcinoembryonic antigen (CEA) level in patients with stage I-III colorectal cancer. **Methods** The clinicopathological data and prognosis were retrospectively analyzed for 393 patients with colorectal cancer treated in our hospital from January, 2003 to December, 2013. Of these patients, 136 had elevated serum CEA level (≥5 ng/mL) and 257 did not show serum CEA elevation (<5 ng/mL). **Results** The two groups of patients showed significant differences in the tumor size, degree of tumor differentiation and lymph node metastasis (*P*<0.05). Cox proportional hazards model suggested that an elevated preoperative CEA level was a risk factor for survival and tumor recurrence, and increased the risks of death and tumor recurrence by 1.59 and 1.89 folds, respectively. Compared with the patients without CEA elevation, those with elevated CEA level had a significantly higher mortality rate (28.7% *vs* 19.8%, *P*<0.05) and tumor recurrence rate (32.4% *vs* 19.1%, *P*<0.05) with a significantly lower cumulative total survival rate and cumulative disease-free survival rate (*P*<0.05); the same results were also found in stage-Ⅲ patients (*P*<0.05). **Conclusions** New survival and recurrence data can be generated by incorporating serum CEA level in TNM staging system for more accurate prognostic assessment of the patients.

Key words: colorectal cancer; carcinoembryonic antigen; prognosis

结直肠癌是常见的恶性肿瘤,我国结直肠癌的发病率在恶性肿瘤中占第3位。对于已明确诊断的结直肠癌病人,对预后做出准确评估具有重要意义。目前临床上主要采用美国癌症联合会(AJCC)的TNM分期系统[1]对结直肠癌的预后进行评估,研究发现,这种基于肿瘤解剖学范围的分期方法可能夸大了肿瘤的生物学潜能及总死亡和复发风险[2],近年来一些与肿瘤侵袭性相关的非解剖学的预测因子被加入TNM分期系统,以增加评估的准确性。大量早期同近期的研究都证实治疗前癌胚抗原(CEA)水平可作为独立的危险因素预测结直肠癌的不良预后[3-8],而AJCC早在15年前就拟将治疗前血清CEA水平(C stage)加入结直肠癌TNM分期系统[9],但缺乏长期生存的数据支持,直到近期来自美国SEER数据库的证据证实在相同TNM分期下,高C stage病人预后差[10],这些研究结果都证实了CEA水平对判断病人的预后的价值。因此,为获得我国结直肠癌病人的相关信息,我们设计此试验,拟对我院收治的TNM Ⅰ~Ⅲ期结直肠癌病人的长期生存数据进行回顾

收稿日期:2016-06-17
基金项目:广州市科技计划项目(2014Y2-00137)
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性分析，目的是通过在TNM分期系统中加入治疗前癌胚抗原水平后重新评估Ⅰ~Ⅲ期结直肠癌病人的预后。

1 研究对象

1.1 一般资料

回顾性分析广州市第一人民医院2003年1月~2013年12月行手术治疗的结直肠癌病人的临床病例资料，病人病历及随访信息完整。病人入选标准：年龄>18岁；术后病理证实的原发性结、直肠腺癌及粘液腺癌；完成肿瘤根治性切除手术；术后对病人行以5-FU为基础的方案辅助化疗。根据治疗前CEA水平将病人分成两组，即升高组（CEA≥5 ng/mL）和未升高组（CEA<5 ng/mL）。

1.2 观察指标

年龄、性别、肿瘤位置、大小、分化程度、TNM分期及术前CEA值。两组病人复发率、复发类型、总死亡率、累计总生存率及累计无瘤生存率。

1.3 随访及统计学方法

末次随访定为2014年8月，总生存时间定义为手术日起至末次随访日或死亡所经历的时间。无瘤生存时间定义为手术日起至肿瘤复发所经历的时间，以月为单位。复发需有明确的影像学或病理学证据支持。计量资料用独立样本t检验或Mann-Whitney U检验，计数资料采用χ^2检验或Fisher确切概率法，用Kaplan-Meier法比较两组病人的累积总生存率、无瘤生存率，用log-rank法检验，COX模型分析影响术后病人生存及复发的危险因素，P值取双尾，P<0.05差异具有统计学意义，所有计算采用spss17.0软件包进行。

2 结果

2.1 两组病人临床、病理数据的比较

查阅病历，提取有完整临床及随访信息的病人共393例，其中升高组136例，未升高组257例，两组病人的肿瘤大小、分化程度、淋巴结转移的差异有统计学意义（P<0.05），两组病人年龄、性别、肿瘤位置、病理类型、浸润深度、TNM分期差异无统计学意义（表1）。

表1 两组病人临床、病理数据的比较

Tab.1 Comparison of clinicopathologic data between the two groups

	CEA<5 ng/mL (*n*=257)	CEA≥5 ng/mL (*n*=136)	χ^2/*t*/*Z*	*P*
Age (year, Mean±SD)	60.4 (11.8)	62.6 (11.6)	1.712	0.088
Gender			1.570	0.210
Male	138 (62.7)	82 (37.3)		
Female	119 (68.8)	54 (31.2)		
Tumour size (cm)	4.39±1.68	5.48±3.52	3.384	0.001
Location of tumour			0.684	0.165
Colon	140 (64.5)	77 (35.5)		
Rectum	117 (66.5)	59 (36.5)		
Pathology			0.726	0.394
Adenocarcinoma	238 (64.9)	129 (35.1)		
Mucinous adenocarcinoma	19 (73.1)	7 (26.9)		
Regression grade scale			7.122	0.028
1	65 (72.2)	25 (27.8)		
2	159 (66.5)	80 (33.5)		
3	33 (51.6)	31 (48.4)		
TNM stage			1.961	0.375
I	4 (44.4)	5 (55.6)		
II	145 (65)	78 (35)		
III	108 (67.1)	53 (32.9)		
IV	0	0		
T classification			1.393	0.262
T1+T2	48 (71.6)	19 (28.4)		
T3+T4	209 (64.1)	117 (35.9)		
N classifi cation			23.95	0.000
N0	164 (75.9)	52 (24.1)		
N1-2	92 (52.3)	84 (47.7)		

2.2 影响结直肠癌术后生存及复发的COX模型分析

以病人的性别、年龄、肿瘤病理类型、肿瘤分化程度、肿瘤大小、肿瘤浸润深度、淋巴结转移及术前CEA水平为自变量进行COX回归分析，结果显示，中或低的肿瘤分化程度，有淋巴结转移，年龄大于60岁及术前高CEA水平是影响病人术后病人生存的危险因素，详见表2；而中或低的肿瘤分化程度、有淋巴结转移，肿瘤浸润肌层以上，年龄大于60岁及术前高CEA水平是影响病人术后病人复发的危险因素（表3）。

表2 影响结直肠癌术后生存的COX模型

Tab.2 Multivariate analysis of the patients' survival

Variable	Category	B Value	Wald Value	df	Sig.	Exp (B)	95% CI
Age (year)	⩾60/<60	0.564	6.095	1	0.014	1.758	0.714-1.687
Regression grade scale	1/2	-1.333	18.54	1	0.000	0.264	0.144-0.484
	1/3	-1.346	28.50	1	0.000	0.260	0.519-0.426
N classification	N1-2/ N0	0.960	17.65	1	0.000	2.612	1.669-4.087
C-stage (ng /mL)	⩾5/<5	0.462	4.292	1	0.038	1.587	1.025-2.456

表3 影响结直肠癌术后复发的COX模型

Tab.3 Multivariate analysis of tumor recurrence in the patients

Variable	Category	B Value	Wald Value	df	Sig.	Exp (B)	95% CI
Age (year)	⩾60/<60	0.492	4.836	1	0.028	1.636	1.055-2.538
Regression grade scale	1/2	-1.499	20.953	1	0.000	0.223	0.118-0.424
	1/3	-1.180	23.308	1	0.000	0.307	0.190-0.496
T classification	T1-2/ T3-4	-0.623	5.520	1	0.019	0.536	0.319-0.902
N classification	N1-2/N0	0.656	8.711	1	0.003	1.972	1.247-2.979
C-stage（ng /mL）	⩾5/<5	0.619	8.009	1	0.005	1.858	1.210-2.853

2.3 两组病人生存及复发的比较

在随访期内，CEA升高组的死亡率及复发率均高于未升高组，差异有统计学意义（P<0.05，表4）。

2.4 两组病人及TNM Ⅰ~Ⅲ期病人累积总生存率及无病生存率的比较

升高组病人的累积总生存率（P=0.006）及累积无瘤生存率（P=0.000）明显低于未升高组病人，差异有统计学意义；TNM Ⅰ~Ⅱ期两组病人的累积总生存率及累积无瘤生存率差异无统计学意义；TNM Ⅲ期升高组病人的累积总生存率及累积无瘤生存率明显低于CEA未升高组病人，差异有统计学意义（P<0.05，图1、2）。

表4 两组病人生存及复发的比较

Tab.4 Comparison of survival and tumor recurrence between the two groups

	CEA<5 ng/mL (n=257)	CEA⩾5 ng/mL (n=36)	χ^2/t	P
Follow-up (month)	55.73±23.92	47.21±27.91	3.019	0.003
Death (%)	51 (19.8)	39 (28.7)	3.929	0.047
Recurrence rate (%)	49 (19.1)	44 (32.4)	8.692	0.003
Recurrence pattern (%)				
Liver metathesis	19 (7.4)	27 (19.8)		
Lung metastases	12 (4.8)	7 (5.1)		
Bone metastases	10 (3.9)	6 (4.4)		
Other	8 (3.1)	4 (2.9)		

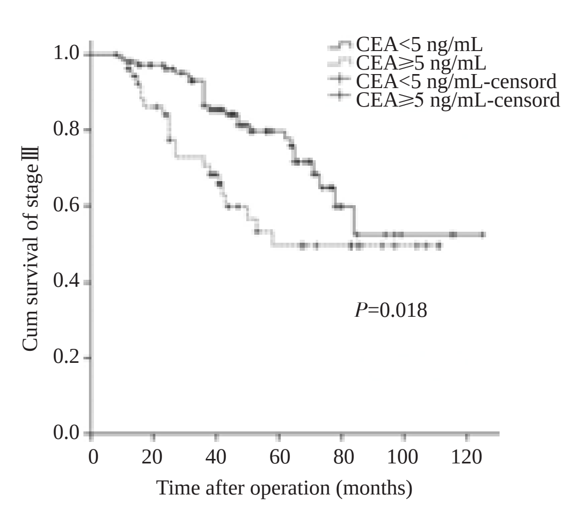


图1 两组Ⅲ期病人累计总生存率比较

Fig.1 Comparison of overall survival between two groups of stage III.

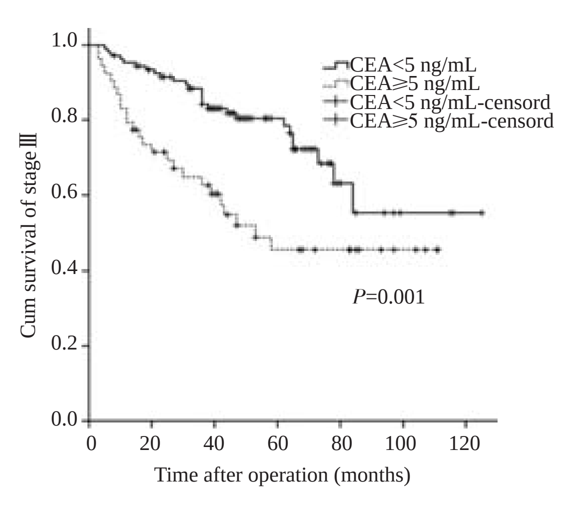


图2 两组Ⅲ期病人累计无瘤生存率比较

Fig.2 Comparison of recurrence-free survival between stage III patients in the two groups.

3 讨论

本文目的旨在探讨治疗前癌胚抗原水平与TNM Ⅰ~Ⅲ期结直肠癌病人预后的关系。研究发现单一的TNM分期方法可能夸大了肿瘤的生物学潜能及总死亡和复发风险，因此，美国癌症联合会通过在TNM分期系统中加入一些肿瘤侵袭性相关的非解剖学的预测因子以增加评估的准确性。鉴于大量研究证实治疗前癌胚抗原水平(C stage)可作为独立的危险因素预测结直肠癌的不良预后[11-14]，因此，根据AJCC结直肠癌组的关于C stage的分类的指导意见将我院收治的393例结直肠癌病人分为未升高组(CEA<5 ng/mL)及升高组(CEA≥5 ng/mL)，其中未升高组136例，升高组257例。

通过对我院病人临床数据回顾性分析发现，升高组病人的肿瘤直径大，分化程度低、常见淋巴结转移，两组间差异有统计学意义(P<0.05)。Huh等[15]研究发现高水平组(CEA≥5 ng/mL)结直肠癌病人肿瘤直径大、T和N分期较晚且阳性的周围神经侵犯，这些指标同CEA水平一样都可以判断结直肠癌病人的不良预后。因此CEA水平越高，结直肠癌病人肿瘤的恶性程度越高，临床分期越晚[16]，死亡率越高[17]。另外，本研究COX回归分析的结果也证实，术前高CEA水平是影响病人术后生存及复发的危险因素，升高组病人死亡及复发风险分别提高1.59及1.89倍。

本研究比较了两组病人的总死亡率及复发率，在随访期内，升高组病人总死亡率(28.7%)高于未升高组病人(19.8%)，且升高组病人复发率(32.4%)高于未升高组病人(19.1%)，差异均有统计学意义(P<0.05)。国外的研究也得出同样结论，Huh等[18]回顾分析了474例病人的生存数据，结果显示血清CEA正常组(CEA<5 ng/mL)患者的五年生存率为81.%，而升高组患者的生存率明显降低，仅为69.9%。Takagawa等[19]对638例病人回顾性分析发现CEA升高组病人(CEA>10 ng/mL)的术后复发率高达41.3%，而CEA未升高组的复发率仅为15.4%。由此可见，CEA水平的升高可预示肿瘤病人的高死亡率及复发率[20-21]。

本文进一步通过Kaplan-Meier法比较两组病人的累积总生存率、无瘤生存率，结果发现，CEA升高组病人的累积总生存率(P=0.006)及累积无瘤生存率(P=0.000)明显低于CEA未升高组病人，差异有统计学意义。对病人分期后再对上述指标比较发现，在Ⅲ期结直肠癌病人中，CEA升高组病人的累积总生存率(P=0.018)及累积无瘤生存率(P=0.001)明显低于CEA未升高组病人，差异有统计学意义。Wuxiao等[22]的研究发现，在Ⅲ期结直肠癌病人中CEA水平的升高提示结直肠癌病人的不良预后。Lin等[23]对363例Ⅲa期结直肠癌病人的数据进行回顾性分析发现，CEA水平正常组病人的5年总生存率明显高于CEA水平升高组。因此，对Ⅲ期结直肠癌病人，联合C stage可更准确的判断病人的预后。

综上所述，在TNM分期系统中加入C stage后可产生新的生存及复发数据，指导临床医生更准确的判断病人的预后。

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（编辑:孙昌朋）